REMARKS

At the outset, Applicant wishes to thank Examiner Robinson and Examiner Wax for the courtesies extended during the telephone calls with Applicant's representatives on January 15, 2004, January 16, 2004, and January 22, 2004.

The specification has been amended to update the continuity data. Specifically, the specification has been amended to indicate that U.S. application Serial No. 09/470,662, filed on December 22, 1999, has issued as U.S. Patent No. 6,268,390.

Claims 21-47 and 49-55 were pending in this application. On January 15, 2004, Examiner Robinson telephoned Attorneys for Applicant and indicated that restriction of the claims to one of two groups is required under 35 U.S.C. §121. On January 16, 2004, Attorneys for Applicant telephoned Examiner Robinson and made a provisional election without traverse to prosecute Group II claims, *i.e.*, claims 50-55. Applicant hereby affirms the provisional election and acknowledge the withdrawal of claims 21-47 and 49 from further consideration in this application, as being drawn to a non-elected invention.

On January 22, 2004, Examiner Robinson and Examiner Wax telephoned Attorneys for Applicant and indicated that the application is free of the prior art but that claim 50 and others needs to be amended to overcome issues under 35 U.S.C. §112, first and second paragraphs. Specifically, Examiner Wax proposed that Applicant amend claim 50 to specifically recite the therapeutic agent. In addition, Examiner Robinson informed Attorneys for Applicant that a new Oath needs to be submitted to reflect the deletion of six previously named inventors. Because Attorneys for Applicant indicated to the Examiners that they will need time to discuss these issues with the Applicant, the present Office Action was issued.

Claims 21-47 and 49 have been canceled. Applicant reserves the right to prosecute the subject matter of the canceled claims in one or more related applications. Claims 50, 51 and 54 have been amended to clarify the present invention. The amended claim is fully supported by the instant specification as originally filed and, as such, do not constitute new matter. Upon entry of the present amendments, claims 50-55 will be pending in this application.

Specifically, the term "a free, non-binding partner associated therapeutic agent" in claim 50 has been replaced with the term "a free therapeutic agent", *i.e.*, one that is not associated with a targeted or binding partner. Support for amended claim 50 can be found in the specification at, *inter alia*, page 1, lines 19-25; page 6, lines 14-20; page 9, line 10 to page 10, line 5; and page 17, lines 13-14. Claims 52 and 54 have been amended to correct the recitation of the antecedent term "free therapeutic agent." No new matter has been added.

I. THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The specification is objected to because page 1 allegedly does not accurately report the continuity data.

Applicant has amended the specification to update the continuity data. Specifically, the specification has been amended to indicate that U.S. application Serial No. 09/470,662, filed on December 22, 1999, has issued as U.S. Patent No. 6,268,390. Applicant submits that the amended specification accurately reports the continuation data. As such, the objection to the specification should be withdrawn.

II. THE REQUEST FOR A NEW OATH/DECLARATION SHOULD BE WITHDRAWN

The Examiner asserts that Applicant failed to file a new Oath/Declaration in connection with a previously filed petition under 37 C.F.R. §1.48(b) to correct inventorship. The Examiner requests a new Oath/Declaration to be filed. For the following reasons, Applicant respectfully declines.

37 C.F.R. §1.48(b) states that when amendment or cancellation of claims results in fewer inventors, amendment of the inventorship requires:

> (1) A request, signed by a party set forth in §1.33(b), to correct the inventorship that identifies the named inventor or inventors being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application; and
> (2) The processing fee set forth in §1.17(i).

37 C.F.R. §1.48(b) does not require that a new Oath/Declaration be filed in connection with a filed petition under 37 C.F.R. §1.48(b) to correct inventorship. As such, Applicant submits that the Examiner's request that a new Oath/Declaration is required was issued in error and should be withdrawn.

More specifically, pursuant to 37 C.F.R. §1.48(b)(1), on October 10, 2001, Applicant filed a Petition to Correct Inventorship Pursuant to 37 C.F.R. §1.48(b) requesting that the names of Richard A. Klein, John M. Reno, David J. Grainger, James C. Metcalfe, Peter L. Weissberg, and Peter G. Anderson be deleted as co-inventors in the application. The inventors were correctly named as inventors in the application as filed, but prosecution of the present application resulted in the cancellation of claims so that certain of the originally named inventors are no longer inventors of the currently claimed subject matter. In particular, the inventor of the currently claimed subject matter is Lawrence L. Kunz.

Pursuant to 37 C.F.R. §1.48(b)(2) and §1.17(i), when Applicant filed the Petition on October 10, 2001, Applicant also authorized the Patent Office to charge the required fee of $130.00 for submission of the Petition.

Applicant submits that all of the requirements of 37 C.F.R. §1.48(b) have been satisfied. Based on the foregoing, it is respectfully requested that the Petition under 37 C.F.R. §1.48(b) be granted and that the subject application be amended to reflect the correct inventor, *i.e.*, Lawrence L. Kunz.

III. THE OBJECTION TO THE INFORMATION DISCLOSURE STATEMENTS SHOULD BE WITHDRAWN

The Examiner states that the Information Disclosure Statement filed on March 12, 2003 fails to comply with the provisions of 37 C.F.R. §1.97 and §1.98 and MPEP 609 because there are items listed on the Information Disclosure Statement that are missing from the application. For the following reasons, Applicant respectfully disagrees.

37 C.F.R. §1.56 requires that each individual associated with the filing or prosecution of a patent application comply with a duty to disclosure all information known to be material to the patentability of the pending claims. Pursuant to 37 C.F.R. §1.56(a), the duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim was submitted to the Patent Office in the manner prescribed by §§1.97(b)-(d) (entitled "Filing of Information Disclosure Statement") and 1.98 (entitled "Content of Information Disclosure Statement").

Pursuant to 37 C.F.R. §1.97(b), an information disclosure statement shall be considered by the Patent Office if filed by the Applicant before the mailing of a first Office action on the merits. Pursuant to 37 C.F.R. §1.98(a), any information disclosure statement filed under 37 C.F.R. §1.97 shall include (1) a list of all patents, publications, applications, or other information submitted for consideration by the Patent Office; and (2) a legible copy of (i) each U.S. patent application publication and U.S. and foreign patent; (ii) each publication or that portion which caused it to be listed; (iii) the application specification and any drawing of each cited pending U.S. application, or that portion which caused it to be listed; and (iv) all other information or that portion which caused it to be listed.

The relevant Rules of Practice, *i.e.*, 37 C.F.R. §§1.56, 1.97 and 1.98, do not require that items listed on the Information Disclosure Statement be found in the application. As such, Applicant submits that the Examiner's objection to the Information Disclosure Statement was issued in error and should be withdrawn.

On July 20, 2001, Applicant submitted an Information Disclosure Statement and a revised PTO Form 1449 listing a number of documents. On January 15, 2002, Applicant submitted a first Supplemental Information Disclosure Statement, a revised PTO Form 1449 listing five documents, and copies of the five listed documents. On March 12, 2002, Applicant submitted a second Supplemental Information Disclosure Statement, a revised PTO Form 1449 listing seven documents, and copies of the seven listed documents. On June 18, 2002, Applicant submitted a third Supplemental Information Disclosure Statement, a revised PTO Form 1449 listing thirty documents, and copies of the thirty listed documents. On March 5, 2003, Applicant submitted a fourth Supplemental Information Disclosure Statement, a revised PTO Form 1449 listing thirty-three documents, and copies of the thirty-three listed documents.

The first Office action on the merits was mailed by the Patent Office on January 28, 2004. As such, the Information Disclosure Statement and the first, second, third, and fourth Supplemental Information Disclosure Statement were all filed before the mailing of the first Office action on the merits. Pursuant to 37 C.F.R. §1.97(b), the Information Disclosure Statement and the first, second, third, and fourth Supplemental Information Disclosure Statements should be considered by the Patent Office.

The Information Disclosure Statement listed only those documents previously cited by or submitted to the Patent Office in connection with an earlier U.S. application, which is relied upon for an earlier filing date under 35 U.S.C. §120. Pursuant to 37 C.F.R. §1.98(d), Applicant did not provide copies of the listed documents. The first, second, third, and fourth Supplemental Information Disclosure Statements listed documents that were not previously cited by or submitted to the Patent Office in connection with an earlier U.S. application. Pursuant to 37 C.F.R. §1.98(a)(2), Applicant submitted a legible copy of (i) each U.S. patent application publication and U.S. and foreign patent; (ii) each publication or that portion which caused it to be listed; (iii) the application specification and any drawing of each cited pending U.S. application, or that portion which caused it to be listed; and (iv) all other information or that portion which caused it to be listed. Applicant submits that none of the cited documents was written in a non-English language and therefore, did not required the submission of a concise explanation of its relevance or an English translation thereof.

Applicant submits that all of the requirements of 37 C.F.R. §§1.56, 1.97 and 1.98 have been satisfied. Based on the foregoing, it is respectfully requested that all of the items listed on the Information Disclosure Statement and the first, second, third, and fourth Supplemental Information Disclosure Statements be considered.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected claims 50-55 under 35 U.S.C. §112, first paragraph ("Section 112, ¶1"), because the specification is allegedly not enabled for the full scope of the claim. Specifically, the Examiner acknowledges that while the specification is enabled for a method to reduce restenosis, it is allegedly not fully enabled for any or all therapeutic agent that inhibits vascular smooth muscle cell migration as claimed.

Applicant respectfully asserts that for the following reasons, the instant specification does indeed fully enable one of skill in the art to practice the claimed invention.

1. The Legal Standard

The enablement requirement refers to the requirement of 35 U.S.C. §112, first paragraph, that the specification describes (1) how to make and (2) how to use the invention. *See* MPEP §2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 U.S.P.Q. 276, 279 (CCPA 1971). The factors that are relevant in determining what constitutes undue experimentation as set forth in *Wands* (citing *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)) include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d 731, 740, 8 USPQ2d 1400, 1406 (Fed. Cir. 1988).

The Patent Office must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement

requirement of §112, the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Patent Office's *prima facie* case should address each of the *Wands* factors since "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others." *See* MPEP §2164.01(a), citing *Wands* at 1407. Where the Patent Office does not provide evidence regarding one or more *Wands* factors, Applicant presumes that such factors support the conclusion that the claims at issue are fully enabled.

2. The Present Invention

The present invention relates to a novel method for reducing restenosis following a vascular surgical procedure (*e.g.*, angioplasty) by locally administering to a human a biocompatible, non-biodegradable sustained release dosage form that comprises a cytostatic amount of a free therapeutic agent dispersed in a polymer-containing matrix (claim 50). Specifically, the free therapeutic agent is an agent that is not associated with a targeted or binding partner, inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. More specifically, the free therapeutic agent is to be administered at a cytostatic amount, *i.e.*, an amount that exerts a relatively minimum effect on protein synthesis and a relatively larger effect on DNA synthesis (see, *e.g.*, specification at page 30, lines 30-32 and page 35, lines 5-8). Claims 51-55 depend from claim 50 and, thus, also include the recitation of claim 50.

3. The Specification Fully Enables The Methods Of Claims 50-55

The instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation as explained below. In particular, Applicant submits that one skilled in the art can make and use the invention, including a cytostatic amount of a free therapeutic agent that inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, by using the teaching from the specification *coupled with* information known in the art.

Applicant points out that the Examiner has not made an enablement rejection over the method *as a whole*. "The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent." See MPEP §2164

(emphasis added). The present claims require locally administering to a human a biocompatible, non-biodegradable sustained release dosage form comprising a cytostatic amount of a free therapeutic agent dispersed in a polymer-containing matrix, said therapeutic agent inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis (claim 50). Thus, the therapeutic agent is not just any therapeutic agent as the Examiner alleges, but a *free* therapeutic agent that *inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis.* Likewise, the amount of therapeutic agent used is not an unspecific amount as the Examiner alleges, but a *cytostatic* amount that exerts a relatively minimum effect on protein synthesis and a relatively larger effect on DNA synthesis (see, *e.g.*, specification at page 30, lines 30-32 and page 35, lines 5-8).

The Examiner applied five *Wand* factors under the test for undue experimentation. First, the Examiner alleges that one of skill in the art would have to engage in undue experimentation to determine if all therapeutic agents that suppresses or inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity and does not substantially inhibit protein synthesis and is a free non-binding partner associated therapeutic agent absence guidance/direction.

Contrary to the Examiner's allegation, the specification is not absent in guidance or direction. Rather, as discussed in detail below, the specification clearly teaches and fully describes examples of a number of free therapeutic agents (see, *e.g.*, page 7, line 11 to page 8, line 14; page 17, line 13 to page 22, line 11; page 30, line 24 to page 36, line 27), how to determine whether a free therapeutic agent inhibits smooth muscle cell migration (see, *e.g.*, page 16, lines 18-24; Example 11), how to determine whether a free therapeutic agent does not exhibit substantial cytotoxicity (see, *e.g.*, page 35, lines 6-8; Example 8), and how to determine whether a free therapeutic agent does not substantially inhibit protein synthesis (see, *e.g.*, page 34, lines 29-33; Example 8).

More importantly, Applicant submits the claims do not relates to the use of any or all therapeutic agents as the Examiner alleges. Instead, the claims are directed to the use of those free therapeutic agents that inhibit vascular smooth muscle cell migration, do not exhibit substantial cytotoxicity, and do not substantially inhibit protein synthesis. Applicant submits that although *some* experimentation might be necessary to practice the present invention, the quantity of experimentation necessary is not unduly burdensome to one of skill in the art.

Enablement is not precluded even if *some* experimentation is necessary, as long as the amount of experimentation needed is not unduly extensive. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Applicant submits that based on the teachings of the specification and information known in the art, one skilled in the art would know how to determine whether a free therapeutic agent inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. It would be well within the abilities of the skilled artisan to be able to apply and monitor biological assays that measure smooth muscle cell migration, protein synthesis inhibition, and DNA synthesis inhibition. Thus, contrary to the Examiner's allegation, the determination of the free therapeutic agent in the claimed methods does not require *undue* experimentation.

Second, the Examiner alleges that the amount of direction or guidance presented in the specification to be able to practice the claimed invention is inadequate based on the absence of exemplification of all the compounds that are considered to be a therapeutic agent.

Contrary to the Examiner's allegation, the specification is not inadequate. Not only does the specification clearly teach and fully describe a number of free therapeutic agents and how to determine which of these free therapeutic agents suppresses or inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, the specification also provides exemplification of a number of compounds that are considered to be the free therapeutic agents of interest.

As a preliminary matter, the specification teaches many different classes of free therapeutic agents that may be useful in the present invention, *e.g.*, page 4, lines 32-34 (therapeutic agents that alter cellular metabolism, inhibit protein synthesis, cellular proliferation or cell migration); page 4, lines 34-36 (microtubule and microfilament inhibitors that affect morphology or increases in cell volume); page 4, line 36 to page 5, line 1 (inhibitors of extracellular matrix synthesis or secretion); page 5, lines 6-7 (protein kinase inhibitors); page 5, lines 7-8 (TGF-beta activators or production stimulators); page 5, lines 10-11 (nitric oxide releasing compounds); page 5, lines 15-18 (therapeutic agents that inhibit the contraction or migration of smooth muscle cells and maintain an enlarged luminal area following, for example, angioplasty trauma); page 30, lines 30-34 (a "cytostatic agent"); page

30, line 35 to page 31, line 1 (an "anti-migratory agent"); page 31, lines 1-4 (a "cytoskeletal inhibitor" or "metabolic inhibitor"); page 31, lines 4-6 (an "anti-matrix agent").

Moreover, the specification teaches a number of preferred free therapeutic agents, *e.g.*, page 5, lines 6-7 (staurosporin, suramin); page 5, lines 9-10 (tamoxifen, TGF-beta); page 5, line 11 (nitroglycerin); page 5, lines 14-15 (taxol, taxotere); page 5, lines 18-20 (cytochalasin B, cytochalasin C, cytochalasin D); page 7, lines 31-32 (roridin A, *Pseudomonas* exotoxin); page 8, line 5 (sphingosine); page 8, lines 11 (somatostatin, N-ethylmaleimide); page 31, line 8 to page 32, line 3 ("cytostatic agents"); page 32, lines 4-16 ("anti-migratory agents"); page 32, lines 17-20 ("cytoskeletal inhibitors"); page 32, line 21 to page 34, line 2 ("metabolic inhibitors"); and page 34, lines 3-17 ("anti-matrix agents").

In addition, the specification also teaches how to determine whether a free therapeutic agent suppresses or inhibits vascular smooth muscle cell migration. For example, the specification teaches that migration of smooth muscle cells may be studied *in vitro* by following the motion of a cell from one location to another using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time (see page 16, lines 18-24). The extent of smooth muscle cell migration inhibition can be measured using scratch assays (see Example 11).

The specification additionally teaches how to determine whether a free therapeutic agent exhibit substantial cytotoxicity. For example, the specification teaches that therapeutic agents exert minimal cytotoxicity (*i.e.*, does not exhibit substantial cytotoxicity) at concentrations where significant DNA synthesis inhibition occurs (see page 35, lines 6-8). The level of DNA synthesis inhibition can be measured using the ^{3}H-thymidine DNA synthesis inhibition assay (see Example 8).

Furthermore, the specification teaches how to determine whether a free therapeutic agent substantially inhibit protein synthesis. For example, the specification teaches that therapeutic agents exert minimum protein synthesis inhibition (*i.e.*, does not substantially inhibit protein synthesis) at concentrations that do not kill the target cells (see page 34, lines 29-33). The level of protein synthesis inhibition can be measured using the ^{3}H-leucine protein inhibition assay (see Example 8).

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added). Here, the specification not only provides a comprehensive list of possible compounds that may be useful in the claimed methods, but it

also fully teaches how to identify which free therapeutic agents inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis.

In addition, the specification provides four specific examples of free therapeutic agents that are useful in the claimed method, *i.e.*, suramin, staurosporin, nitroglycerin, and cytochalasin B (see Example 8). Moreover, the specification provides exemplification on how to determine whether a free therapeutic agent inhibits smooth muscle cell migration (see Example 11), does not exhibit substantial cytotoxicity (see Example 8), and does not substantially inhibit protein synthesis (see Example 8).

Applicant submits that the amount of direction and guidance presented in the specification is more than sufficient. As noted, the claims do not relate to the use of any or all therapeutic agents as the Examiner alleges. Instead, the claims only relate to the use of those free therapeutic agents that inhibit vascular smooth muscle cell migration, do not exhibit substantial cytotoxicity, and do not substantially inhibit protein synthesis. As such, the teaching of the specification bears a reasonable correlation to the entire scope of the claim. Finally, Applicant submits that one skilled in the art can make and use the invention including identifying the therapeutic agent to be used and the amount of the therapeutic agent to be used to reduce restenosis, without undue experimentation, by using the teachings from the specification *coupled with* information known in the field.

Third, the Examiner alleges that the working examples provided does not rectify the problem of breath in the claims. The Examiner states that the claims are not supported by the instant specification, "as the unspecified amount of therapeutic agents having the effect as claimed is not supported by the disclosure." Contrary to the Examiner's allegation, the cytostatic amount of therapeutic agents having the effect as claimed is supported by the disclosure. Attention is directed to page 7, lines 15-18, page 35, lines 5-8, and page 34, lines 29-33, respectively, which state that the therapeutic agents inhibit cell migration, exert minimal cytotoxicity, and do not significantly inhibit protein synthesis. Attention is further directed to page 5, lines 4-6, which states that the amounts of free therapeutic agents useful in the claimed methods are those that have a minimal effect on protein synthesis and is not cytotoxic, and page 68, lines 12-16, which states that the differential between ^{3}H-leucine uptake (a measure of protein inhibition) and ^{3}H-thymidine uptake (a measure of DNA synthesis inhibition) is what makes a free therapeutic agent cytostatic at certain doses. In other words, the specification teaches that a cytostatic amount of a free therapeutic agent inhibits DNA synthesis more than it inhibits protein synthesis (see page 35, lines 5-8; and

page 108, lines 14-17). Specifically, the specification further provides exemplifications of ranges of cytostatic amounts for four free therapeutic agents (*i.e.*, suramin, staurosporin, nitroglycerin, and cytochalasin B) (see Tables 10A-D).

Furthermore, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d at 740, 8 USPQ2d at 1407. The absence of an illustrative examples is not determinant on whether undue experimentation is required. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Nevertheless, contrary to the Examiner's allegation, the specification does provide examples on how to determine a cytostatic amount of a free therapeutic agent.

Applicant submits that in view of the present specification and the knowledge in the art the identification of appropriate therapeutic agents that inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, and the determination of the amount of the therapeutic agent that exerts a minimum effect on protein synthesis and relatively more effect on DNA synthesis inhibition as known to one skilled in the art. Moreover, the skilled artisan in the art would certainly realize that exposure to any free therapeutic agent to abnormally high doses could be detrimental and possibly cytotoxic to the cells. The kind of free therapeutic agent and the amount of said free therapeutic agent that would be damaging to the vascular smooth muscle cell can be determined by simple trial and error and would be somewhat intuitive to one of ordinary skill in the relevant art. As such, Applicant submits that it would be routine experimentation for one of ordinary skill in the relevant art to determine (1) which therapeutic agents may be used in the method claims; and (2) how much of the therapeutic agents are to be used in the method claims (*i.e.*, a cytostatic amount), particularly given the teachings of the specification. The use of a cytostatic amount of a free therapeutic agent is neither indefinite nor overly broad as to require undue experimentation to determine. Contrary to the Examiner's allegation, the specification discloses methods for using the claimed invention that bears a reasonable correlation to the entire scope of the application disclosure which is enabling.

Fourth, the Examiner alleges that the claimed invention is directed to a method to reduce restenosis and the metes and bounds of the claims are undefined as the claim encompasses an unlimited amount of therapeutic agents not disclosed or supported. Also, the

Examiner alleges that it is known in the prior art that heparin suppresses smooth muscle cell proliferation and it is disclosed in the instant specification that heparin has a short pharmacological half life thus problematic, yet this is encompassed in the broad claim language of "a free . . . therapeutic agent."

As discussed above, the claimed invention is not directed to the use of any therapeutic agent. Instead, the claimed methods relate to the use of a free therapeutic agent that inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. The specification teaches a number of compounds (including heparin) that may be selected as a free therapeutic agent to be used in the claimed method. Using the teaching of the specification and information available in the art, one reasonably skilled in the art would be able to determine which compound is suitable for use in the claimed method. This is sufficient to satisfy the enablement requirement. As such, Applicant submits that it is irrelevant as to whether heparin may or may not have certain disadvantages even though it can be used in the claimed invention.

Fifth, the Examiner argues that the specification provides several examples of compounds that, although included in the breadth of claim 50, have adverse effects and thus would not be desirable to practice the claimed method.

As discussed above, the claimed invention is not directed to the use of any therapeutic agent. Instead, the claimed methods relate to the use of a free therapeutic agent that inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. Applicant submits that it is irrelevant as to whether certain compounds encompass by the claims that have certain adverse effect. One skilled in the art can choose not to use these compounds in the claimed method.

Applicant submits that when all of the *Wands* factors are considered, one of ordinary skill in the art can determine without undue experimentation those therapeutic agents and amount of the therapeutic agents that would be sufficient to produce the claimed effect, *i.e.*, reduce restenosis. These *Wands* factors are as follows: First, the quantity of experimentation necessary is routine and not unduly extensive. Second, the amount of direction or guidance presented is sufficient. Third, the specification provides a number of working examples of the method of the present invention. Fourth, the state of the art for determining whether a therapeutic agent inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, and the dose at which a therapeutic agent is cytostatic shows that the claims are enabled. Fifth, the relative skill of those in the art is high in terms of practicing and monitoring the molecular scratch assay, the

^{3}H-leucine protein synthesis inhibition assay, and the ^{3}H-thymidine DNA synthesis inhibition assay. Sixth, the art of determining whether a therapeutic agent inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, and the dose at which a therapeutic agent is cytostatic are predictable in view of the specification and knowledge in the art. Finally, the breadth of the claims is reasonable and not overly broad.

Applicant submits that one of ordinary skill in the relevant art would know which therapeutic agents may be used in the claimed methods, *i.e.*, an agent that inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. Applicant also submits that one of ordinary skill in the relevant art would know how much of the therapeutic agent is a cytostatic amount, *i.e.*, the amount that exerts minimum effect on protein synthesis and relatively more effect on DNA synthesis inhibition. Accordingly, the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.

As such, Applicant respectfully requests that the rejection of claims 50-55 under Section §112, ¶1, be withdrawn.

V. THE CLAIM REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected claims 50-55 under 35 U.S.C. §112, first paragraph ("Section 112, ¶2"), as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

First, the Examiner alleges that claim 50 and the dependent claims hereto are indefinite because the claim recites "a free, non-binding partner associated therapeutic agent" and it is unclear what is "an associated therapeutic agent." To clarify the present invention, Applicant has amended claim 50 to recite "a free therapeutic agent", *i.e.*, one that is not bound/conjugated to another partner (see, *e.g.*, specification at page 9, lines 10-13).

Second, the Examiner alleges that claim 51 lacks antecedent basis for the recitation of "therapeutic agent" when the independent claim recites "a free non-binding partner associated therapeutic agent." To clarify the present invention, Applicant has amended claim 51 to recite "free therapeutic agent", the antecedent basis of which can be found in the amended independent claim 50. Similarly, Applicant has amended claim 54 to correct the recitation of the antecedent term "free therapeutic agent."

Third, the Examiner alleges that claim 55 is indefinite because the claim, by reciting that the locally administering can also occur during the vascular procedure, appears to be a prevention rather than a reduction step as recited in the independent claim 50. Contrary to the Examiner's assertion, the administration of the dosage form during the vascular procedure does not necessarily result in prevention of restenosis. For instance, while the restenosis occurs after the vascular procedure, the dosage form can be administered prior to the occurrence of the restenosis, *i.e.*, during the vascular procedure, and the therapeutic agent be slowly released (sustained release) afterwards to reduce the restenosis. Applicant respectfully submit that one skilled in the art, when reading claim 55, would find the claim language neither unclear nor indefinite. As such, the rejection was in error and should be withdrawn.

Applicant respectfully submits that the amended claims are no longer indefinite and respectfully requests that the claim rejections under Section 112, ¶2, be withdrawn.

CONCLUSION

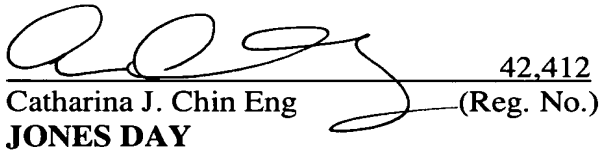
As all objections and rejections are believed to be overcome, all claims are believed to be in condition for allowance. An early notice to that effect would be appreciated. Should the Examiner not agree with Applicant's position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application. No fee aside from the fee associated with the filing of the Petition for Extension of Time submitted herewith is believed to be due. If any such fees are due, please charge the required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: June 22, 2004

27,469
Gidon D. Stern (Reg. No.)

By:



42,412
Catharina J. Chin Eng (Reg. No.)

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Enclosures